A Prospective Study of Body Mass Index, Weight Change, and Risk of Stroke in Women

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Objective.—To examine the associations of body mass index (BMI) and weight change with risk of stroke in women.

Setting and Design.—Prospective cohort study among US female registered nurses participating in the Nurses' Health Study.

Participants.—A total of 116 759 women aged 30 to 55 years in 1976 who were free from diagnosed coronary heart disease, stroke, and cancer.

Main Outcome Measure.—Incidence of ischemic stroke, hemorrhagic stroke (subarachnoid or intraparenchymal hemorrhage), and total stroke.

Results.—During 16 years of follow-up, 866 total strokes (including 403 ischemic strokes and 269 hemorrhagic strokes) were documented. In multivariate analyses adjusted for age, smoking, postmenopausal hormone use, and menopausal status, women with increased BMI (≥27 kg/m²) had significantly increased risk of ischemic stroke, with relative risks (RRs) of 1.75 (95% confidence interval [CI], 1.17-2.59) for BMI of 27 to 28.9 kg/m²; 1.90 (95% CI, 1.28-2.82) for BMI of 29 to 31.9 kg/m²; and 2.37 (95% CI, 1.60-3.50) for BMI of 32 kg/m² or more (*P* for trend<.001), as compared with those with a BMI of less than 21 kg/m². For hemorrhagic stroke there was a nonsignificant inverse relation between obesity and hemorrhagic stroke, with the highest risk among women in the leanest BMI category (*P* for trend=.20). For total stroke the RRs were somewhat attenuated compared with those for ischemic stroke but remained elevated for women with higher BMI (*P* for trend<.001). In multivariate analyses that also adjusted for BMI at age 18 years, weight gain from age 18 years until 1976 was associated with an RR for ischemic stroke of 1.69 (95% CI, 1.26-2.29) for a gain of 11 to 19.9 kg and 2.52 (95% CI, 1.80-3.52) for a gain of 20 kg or more (*P* for trend<.001), as compared with women who maintained stable weight (loss or gain <5 kg). Although weight change was not related to risk of hemorrhagic stroke (*P* for trend=.20), a direct relationship was observed between weight gain and total stroke risk (*P* for trend<.001).

Conclusions.—These prospective data indicate that both obesity and weight gain in women are important risk factors for ischemic and total stroke but not hemorrhagic stroke. The relationship between obesity and total stroke depends on the distribution of stroke subtypes in the population.

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THE PREVALENCE of obesity in the United States has increased steadily over the last several decades, particularly in women.[1] Obesity is an important cause of coronary heart disease,[2-5] as well as several stroke risk factors, including diabetes mellitus[6] and hypertension[7]; however, whether obesity increases risk of stroke remains controversial, especially in women, among whom data are sparse. Only 1 study in women has found a significantly increased risk of stroke,[5] whereas other investigations have shown no association.[8-12] In men, several studies have shown increased risk of stroke, especially ischemic stroke, with increasing adiposity.[13-17] Although weight gain in adults has been associated with increased risk of coronary heart disease,[2,4,5] few studies[18] have evaluated risk of stroke.

Prior studies have infrequently examined stroke subtypes, although there is evidence that obesity and other risk factors might have different effects on various subtypes.[18] Some studies have relied on mortality data[14,15] that overrepresent hemorrhagic stroke. Others have inappropriately controlled for biological mediators in the causal pathway of the effects of obesity, such as high cholesterol, hypertension, and diabetes. In this study, we prospectively examined the relationship of obesity and weight change with risks of ischemic, hemorrhagic, and total stroke during 16 years of follow-up in a large cohort of women in the Nurses' Health Study.

METHODS

The Nurses' Health Study cohort was established in 1976 when 121 700 female registered nurses aged 30 to 55 years answered a questionnaire regarding their

medical history and health behaviors. Further details about the study have been published elsewhere.[2,3,6,19] The 116 759 women who in 1976 were free from cardiovascular disease, stroke, and cancer (except nonmelanoma skin cancer) were included in these analyses.

Risk Factors

In 1976 we asked participants to report their age, current height and weight, current and past cigarette smoking history, and other risk factors as well as personal history of coronary heart disease, stroke, high blood pressure, elevated cholesterol, and diabetes. On follow-up questionnaires, mailed every 2 years, we elicited updated information on risk factors and ascertained the diagnosis of any new medical conditions. In 1980, participants were asked to report their weight at age 18 years, to provide information on physical activity, alcohol consumption, and aspirin use, and to complete a semiquantitative food frequency questionnaire. An antioxidant vitamin score, used in energy-adjusted quintiles, was derived by summing the dietary and supplemental intakes of ascorbic acid, vitamin E, β-carotene, and riboflavin reported on the food frequency questionnaires. Risk factor data were updated for each available questionnaire cycle.

Documentation of Cerebrovascular Disease

All nonfatal and fatal strokes occurring after the return of the 1976 questionnaire but before June 1, 1992, were included in these analyses. Women who reported stroke on follow-up questionnaires were asked for permission to review medical records, which were reviewed by a physician without knowledge of the participant's exposure status. Cerebrovascular pathology due to infection, trauma, or malignancy was excluded, and "silent" strokes discovered only by radiological imaging also were excluded. Stroke was classified according to criteria established by the National Survey of Stroke,[20] which required evidence of a neurologic deficit with sudden or rapid onset that persisted for more than 24 hours or until death. Strokes were classified as follows: ischemic stroke, due to thrombotic or embolic occlusion of a cerebral artery; hemorrhagic stroke, due to either subarachnoid or intraparenchymal hemorrhage; or stroke of unknown subtype, including documented strokes for which the subtype could not be ascertained. The primary end points for this study were ischemic, hemorrhagic, and total stroke. Total stroke analyses include all stroke subtypes: ischemic, hemorrhagic, and strokes of unknown subtype.

Cases in which medical record release was refused or for which medical records were unavailable were classified as probable, if supporting information was provided. Of 678 nonfatal strokes, 169 (24.9%) were classified as probable, with 75 corroborated by letter, 71 by telephone, and 23 as an additional diagnosis on a subsequent death certificate.

Deaths were detected through information provided by the next of kin or postal authorities or by systematic searches of the National Death Index. Follow-up for fatal events has been estimated as more than 98% complete in this cohort.[21] Classification of fatal stroke was confirmed by review of hospital records, autopsy, or death certificate. If information was limited to death certificate or information provided by next of kin, cases were classified as probable. Of 188 fatal strokes, 54 (28.7%) were classified as probable, with 15 corroborated by telephone information provided by next of kin, 26 solely by death certificate, and 13 by death certificate as well as autopsy or other clinical information. Of 866 total strokes, 646 (74.6%) were confirmed on the basis of medical records, and 220 (25.4%) were classified as probable based on supporting information. Results were comparable for the 646 confirmed and 220 probable cases; thus, confirmed and probable cases were combined for these analyses.

Calculation and Validation of Obesity and Weight Gain

Body mass index ([BMI] self-reported weight in kilograms divided by the square of self-reported height in meters [kg/m^2]) was the primary measure of adiposity in this analysis. This index is minimally correlated with height ($r=-0.03$) and highly correlated with absolute fat mass in women ($r=0.84$-0.91).[22] Body mass index was updated for each time period using the data from the most recent biennial questionnaire. If weight was missing during a particular questionnaire cycle, the most recently provided weight was used; BMI categories of less than 21 kg/m^2, 21 to 22.9 kg/m^2, 23 to 24.9 kg/m^2, 25 to 26.9 kg/m^2, 27 to 28.9 kg/m^2, 29 to 31.9 kg/m^2, and 32 kg/m^2 or more were used for comparison with other studies. The leanest category was always used as the referent category. The uppermost category (≥32 kg/m^2) approximates the 95th percentile in our population, and the leanest (<21 kg/m^2) approximates the 10th percentile.

We also examined the effects of weight gain from age 18 years to study entry. As reported on the 1980 questionnaire, weight at age 18 years was available for 93 337 participants. The 20% of participants who failed to provide this information did not differ significantly from the rest of the cohort with respect to BMI or other risk factors. Weight at age 18 years was subtracted from weight in 1976 to calculate a value for weight change. Weight change was classified as loss of 11 kg or more or loss of 5 to 10.9 kg, or gain of 5 to 7.9 kg, 8 to 10.9 kg, 11 to 19.9 kg, and 20 kg or more. Women with weight change (gain or loss) of less than 5 kg were classified as having "stable" weight and constitute the reference group. All weight change analyses also controlled for BMI at age 18 years.

Self-reported and directly measured weight were highly correlated ($r=0.96$) in a subset of 184 Boston-area participants from this cohort.[19] Measured weight in light clothing averaged 1.5 kg more than the weight reported on the most recent questionnaire (within 6-12 months). The validity of self-reported weight at age 18 years has been examined in the companion Nurses' Health Study II, a cohort of 116 000 women aged 25 to 42 years in 1989. In a sample of 118 participants, self-reported weight at age 18 years was strongly correlated with weight recorded in medical records ($r=0.84$).[23] Weight ascertained by medical records at nursing school was on average 1.4 kg greater than recalled weight, resulting in a mean value for BMI of 22.6 kg/m^2 from medical records as compared with 22.1 kg/m^2 using recalled weight.

Statistical Analyses

The analyses include 16 years of follow-up from 1976 through 1992. At the start of each 2-year follow-up period, women with a prior diagnosis of cardiovascular disease, stroke, or cancer were excluded. Analyses that controlled for physical activity, dietary information, or alcohol consumption were restricted to the 87 437 women with available data. Person-time was calculated for each exposure category from the date of the questionnaire report until the date of stroke, change in exposure status, or June 1, 1992, whichever came first. Incidence rates were calculated by dividing the number of events by the accumulated person-time of follow-up for the women in a given BMI or weight change category. Relative risks (RRs) were adjusted for age in 5-year categories. Because leaner women were much more likely to be current smokers, proportional hazards models were used to control for smoking and other risk factors simultaneously. Because hypertension, diabetes, and elevated cholesterol are biological mediators of the effects of obesity, we did not control for these vari-

Table 1.—Age-Adjusted and Multivariate* Relative Risks (RRs) and 95% Confidence Intervals (CIs) of Ischemic Stroke, Hemorrhagic Stroke,† and Total Stroke by Body Mass Index Category in a Cohort of US Women in the Nurses' Health Study With Follow-up From 1976 to 1992

	Body Mass Index (kg/m²) Category							
	<21‡ (Referent) (312 030 Person-Years)	21 to <23 RR (95% CI) (422 060 Person-Years)	23 to <25 RR (95% CI) (343 016 Person-Years)	25 to <27 RR (95% CI) (233 867 Person-Years)	27 to <29 RR (95% CI) (144 440 Person-Years)	29 to <32 RR (95% CI) (138 657 Person-Years)	≥32 RR (95% CI) (126 093 Person-Years)	Trend Test§ *P* Value
Ischemic Stroke								
No. of cases (n=403)	50	70	76	53	50	51	53	...
Age-adjusted	1.0	0.91 (0.63-1.31)	1.05 (0.74-1.49)	1.00 (0.69-1.46)	1.46 (0.99-2.14)	1.47 (0.99-2.18)	1.79 (1.22-2.63)	<.001
Multivariate	1.0	1.01 (0.70-1.45)	1.20 (0.83-1.71)	1.15 (0.78-1.70)	1.75 (1.17-2.59)	1.90 (1.28-2.82)	2.37 (1.60-3.50)	<.001
Hemorrhagic Stroke								
No. of cases (n=269)	57	65	57	32	18	23	17	...
Age-adjusted	1.0	0.76 (0.53-1.09)	0.76 (0.53-1.10)	0.59 (0.38-0.90)	0.49 (0.29-0.84)	0.69 (0.42-1.12)	0.56 (0.33-0.96)	.01
Multivariate	1.0	0.84 (0.58-1.19)	0.85 (0.59-1.23)	0.68 (0.44-1.06)	0.62 (0.36-1.06)	0.85 (0.52-1.38)	0.73 (0.42-1.26)	.20
Total Stroke‖								
No. of cases (n=866)	137	172	168	121	85	89	94	...
Age-adjusted	1.0	0.83 (0.66-1.04)	0.89 (0.71-1.11)	0.88 (0.69-1.12)	0.94 (0.71-1.24)	1.02 (0.78-1.34)	1.22 (0.94-1.60)	.02
Multivariate	1.0	0.91 (0.73-1.14)	1.00 (0.80-1.26)	1.01 (0.79-1.29)	1.14 (0.87-1.50)	1.28 (0.96-1.68)	1.59 (1.22-2.08)	<.001

*Multivariate model adjusted for age (5-year categories), smoking (never, former, current: 1-14, 15-24, ≥25 cigarettes/d), oral contraceptive use (never, former, current), menopausal status (premenopausal, postmenopausal), hormone replacement therapy (never, former, current), and time period.
†Hemorrhagic stroke includes both subarachnoid and intraparenchymal hemorrhages.
‡Reference category is body mass index of less than 21 kg/m².
§Mantel-extension trend test *P* value.
‖Total stroke includes strokes of unknown subtype, in addition to ischemic and hemorrhagic strokes.

ables in the primary analyses, but we did add them sequentially to multivariate models in secondary analyses. The 95% confidence intervals (CIs) were calculated for all RRs, and the Mantel-Haenszel extension test was used to test for trends across categories.

RESULTS

Women with higher BMI tended to be slightly older, and the prevalence of cardiovascular risk factors also differed by level of adiposity (as shown previously[8]). Smoking and alcohol consumption were inversely associated with adiposity. In 1976, 41% of the leanest women (BMI <21 kg/m²) were current smokers compared with 23% of those in the heaviest BMI strata (≥32 kg/m²) in our cohort. Women in the highest BMI category had prevalence rates of 5.1% for elevated cholesterol level, 32.3% for hypertension, and 6.8% for diabetes compared with rates of 2.3%, 6.5%, and 1.1%, respectively, among the leanest women. Weight change from age 18 years to study entry in 1976 showed a similar relationship to risk factors. Women who gained more than 5 kg from age 18 years to 1976 were more likely to have never smoked, whereas those who lost more than 5 kg were more likely to be current smokers. The prevalence of elevated cholesterol level, hypertension, and diabetes was 2- to 4-fold higher among women who gained 20 kg or more as adults compared with those who maintained stable weights.

During the 16 years of follow-up (1 722 163 person-years), we documented 866 incident cases of stroke, including 403 ischemic (357 thrombotic and 46 embolic strokes), 269 hemorrhagic (177 subarachnoid hemorrhages and 92 intraparenchymal hemorrhages), and 194 strokes of unknown subtype. The age-adjusted RR of ischemic stroke was increased for all categories of BMI that were 27 kg/m² or more (Table 1). The relationship was somewhat stronger for thrombotic than embolic strokes; however, there were few embolic strokes. Multivariate adjustment for multiple risk factors, including age, smoking, menopausal status, and hormone use strengthened the relation and indicated significantly increased risks for women with BMI of greater than 27 kg/m² (*P* for trend<.001). Women with a BMI of 32 kg/m² or more had an RR for ischemic stroke of 2.37 (95% CI, 1.60-3.50) compared with the leanest women. When BMI was tested as a continuous variable, a 1-unit increase in BMI was associated with a 5% increased risk of ischemic stroke (RR, 1.05; 95% CI, 1.03-1.07). Adjustment for smoking, a strong risk factor for ischemic stroke,[24] accounted for most of the change in the multivariate model. The association between obesity and ischemic stroke was strongest among current smokers, although it was significant for all smoking categories (Figure 1). Results were modestly attenuated in the smaller cohort of women with strokes that occurred after 1980 for whom additional covariates were available: alcohol consumption, physical activity, combined supplement and dietary antioxidant vitamin intake, and aspirin use (Table 2). Women with a BMI of more than 32 kg/m² had an RR of 1.82 (95% CI, 1.17-2.84) compared with the leanest women, and the RR of ischemic stroke per unit of BMI was 1.04 (95% CI, 1.02-1.06).

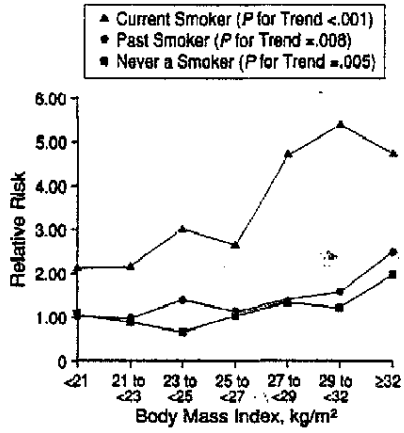

Figure 1.—Age-adjusted relative risk of ischemic stroke according to body mass index and smoking status (1976-1992). Women who were never smokers and had a body mass index of less than 21 kg/m² are the referents. The number of cases among current smokers was 177; past smokers, 107; and among women who were never smokers, 119.

For hemorrhagic stroke the relationship differed (Table 1). In age-adjusted analyses, the risk of hemorrhagic stroke was greatest among women in the leanest BMI category (≤21 kg/m²) with a significant inverse trend (*P* for trend=.01). After multivariate adjustment, the trend was not significant (*P* for trend=.20). Even when examined as a dichotomous variable, BMI of 21 kg/m² or greater was associated with a non-

Table 2.—Multivariate Relative Risks (RRs) and 95% Confidence Intervals (CIs) for Ischemic, Hemorrhagic,* and Total Stroke† by Body Mass Index Category in a Cohort of US Women in the Nurses' Health Study With Follow-up From 1980 to 1992

	Body Mass Index (kg/m²) Category							Trend Test§
	<21‡ (Referent)	21 to <23 RR (95% CI)	23 to <25 RR (95% CI)	25 to <27 RR (95% CI)	27 to <29 RR (95% CI)	29 to <32 RR (95% CI)	≥32 RR (95% CI)	P Value
Ischemic Stroke								
No. of cases (n=306)	40	51	52	42	38	41	42	...
Model (alone)‖	1.0	0.89 (0.59-1.34)	0.95 (0.63-1.43)	1.02 (0.66-1.57)	1.42 (0.91-2.22)	1.62 (1.04-2.51)	1.82 (1.17-2.84)	<.001
With hypertension	1.0	0.86 (0.57-1.30)	0.89 (0.59-1.35)	0.92 (0.59-1.42)	1.22 (0.78-1.92)	1.32 (0.85-2.07)	1.36 (0.86-2.15)	.02
With hypertension, diabetes mellitus, and high cholesterol	1.0	0.85 (0.56-1.28)	0.88 (0.58-1.33)	0.88 (0.57-1.36)	1.12 (0.71-1.83)	1.17 (0.74-1.83)	1.09 (0.69-1.73)	.20
Hemorrhagic Stroke								
No. of cases (n=166)	35	43	31	20	12	14	11	...
Model (alone)	1.0	0.85 (0.54-1.33)	0.68 (0.42-1.10)	0.60 (0.34-1.04)	0.56 (0.29-1.10)	0.70 (0.38-1.33)	0.62 (0.31-1.23)	.08
With hypertension	1.0	0.83 (0.53-1.30)	0.64 (0.39-1.04)	0.54 (0.31-0.93)	0.48 (0.25-0.93)	0.57 (0.30-1.07)	0.43 (0.21-1.87)	.004
With hypertension, diabetes mellitus, and high cholesterol	1.0	0.83 (0.53-1.30)	0.64 (0.39-1.04)	0.54 (0.31-0.94)	0.47 (0.24-0.93)	0.56 (0.29-1.06)	0.41 (0.20-0.84)	.004
Total Stroke								
No. of cases (n=578)	93	115	100	80	63	61	66	...
Model (alone)	1.0	0.86 (0.65-1.14)	0.80 (0.61-1.07)	0.86 (0.64-1.16)	1.06 (0.76-1.48)	1.08 (0.78-1.50)	1.28 (0.93-1.77)	.03
With hypertension	1.0	0.84 (0.64-1.10)	0.76 (0.56-0.99)	0.76 (0.56-1.03)	0.87 (0.63-1.21)	0.84 (0.60-1.18)	0.88 (0.63-1.23)	.70
With hypertension, diabetes mellitus, and high cholesterol	1.0	0.83 (0.63-1.09)	0.74 (0.56-0.98)	0.73 (0.54-0.99)	0.81 (0.59-1.13)	0.76 (0.54-1.06)	0.74 (0.52-1.03)	.12

*Hemorrhagic stroke includes both subarachnoid and intraparenchymal hemorrhages.
†Total stroke includes strokes of unknown subtype, in addition to ischemic and hemorrhagic strokes.
‡Reference category is body mass index of less than 21 kg/m².
§Mantel-extension trend test P value.
‖Multivariate model adjusted for age (5-year categories), smoking (never, former, current: 1-14, 15-24, ≥25 cigarettes/d), oral contraceptive use (never, former, current), menopausal status (premenopausal, postmenopausal), hormone replacement therapy (never, former, current), time period, aspirin use (<1, 1-6, ≥7 tablets/wk), physical activity (<1, 1, 2, 3, ≥4 vigorous episodes/wk), antioxidant score (quintiles, diet and supplements), and alcohol use (0, <1.5, 1.5-4.9, 5.0-14.9, ≥15 g/d).

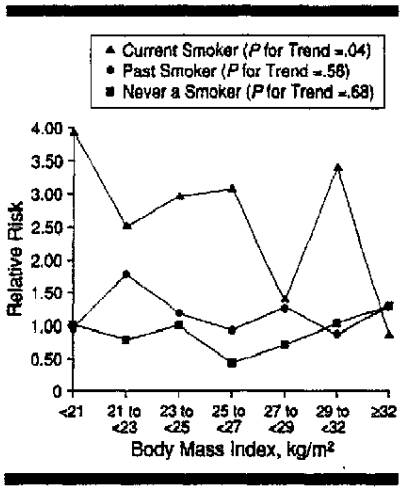

Figure 2.—Age-adjusted relative risk of hemorrhagic stroke according to body mass index and smoking status (1976-1992). Women who were never smokers and had a body mass index of less than 21 kg/m² are the referents. The number of cases among current smokers was 136; past smokers, 67; and among women who were never smokers, 67.

significant RR of 0.78 (95% CI, 0.58-1.05). Adjustment for additional covariates available in 1980 did not materially alter these results (Table 2). In analyses stratified by smoking status, a significant inverse relationship was confined to current smokers, with past smokers and those who were never smokers having nonsignificant inverse trends (Figure 2).

Although the results for ischemic and hemorrhagic stroke were different, we examined the relationship for total stroke to gauge the net impact of BMI on stroke risk and for comparison with other studies that have relied on total stroke. After adjusting for age, women with a BMI of 32 kg/m² or more had an RR of 1.22 (95% CI, 0.94-1.60) for total stroke (Table 1). Multivariate adjustment strengthened the relationship with an RR of 1.59 (95% CI 1.22-2.08) for women in the highest BMI category (P for trend<.001). The RR of total stroke per unit of BMI was 1.03 (95% CI, 1.02-1.04). Results were modestly attenuated with the addition of covariates available in 1980, with women in the highest BMI category having an RR of 1.28 (0.93-1.77) for total stroke compared with the leanest women (Table 2).

We also examined the influence of BMI on fatal and nonfatal strokes. Overall case fatality was 22%, but large differences in case-fatality rates were seen among stroke subtypes. Only 6.5% of ischemic strokes were fatal compared with 54% of hemorrhagic strokes. The age-adjusted and smoking-adjusted risk of nonfatal stroke was directly and significantly related to BMI with an RR of 1.84 (95% CI, 1.34-2.54) for women with a BMI of 32 kg/m² or more compared with the leanest women. Since 75% of fatal strokes were of hemorrhagic origin, the risks of fatal stroke were similar to those for hemorrhagic stroke with a nonsignificant inverse trend (P for trend=.57).

No significant effect modification by age was found for ischemic, hemorrhagic, or total stroke. Results were similar for all stroke subtypes when women younger than 60 years and those 60 years or older were analyzed separately. In addition, excluding the first 4 years of follow-up strengthened the relationship between BMI and ischemic and total stroke, whereas results for hemorrhagic stroke were unchanged.

In our primary analyses, we did not control for biological mediators such as high cholesterol, hypertension, and diabetes because these factors are believed to be intermediate variables in the causal pathway of the effects of obesity. In secondary analyses we explored the residual effects of obesity on stroke after accounting for these mediators. In stratified analyses adjusted for age and smoking, the increased risk of ischemic stroke among obese women appeared confined to those women without previously diagnosed hypertension (Figure 3), suggesting that blood pressure may be a primary mediator of the risk attributable to obesity. In contrast, the inverse association between weight and hemorrhagic stroke was strongest among hypertensive women (Figure 4). We also added these biological mediators stepwise into a proportional hazards model with other covariates that were available from 1980 to 1992 (Table 2). Con-

trolling for hypertension explained much of the increased risk of ischemic stroke observed in the higher BMI categories. After controlling for hypertension, diabetes mellitus, and hypercholesterolemia, only a trend toward increased risk of ischemic stroke was seen with increasing adiposity (P for trend=.20). Adjusting for hypertension and other mediators modestly strengthened the inverse association between BMI and hemorrhagic stroke.

Change in weight from age 18 years to study entry in 1976 also was examined. Adult weight gain was common in our population, with 48% of women gaining more than 5 kg and only 8% losing more than 5 kg from age 18 years until 1976. Weight gain was strongly associated with the risk of ischemic stroke after adjustment for age, BMI at age 18 years, and other risk factors (Table 3). Compared with women who maintained stable weights (gain or loss of less than 5 kg), women who gained between 11 and 19.9 kg or more than 20 kg had RRs for ischemic stroke of 1.69 (95% CI, 1.26-2.29) and 2.52 (95% CI, 1.80-3.52), respectively, after multivariate adjustment (P for trend<.001). Weight change was not related to risk of hemorrhagic stroke (P for trend=.20). For total stroke, a strong direct relationship was seen between weight gain and risk of stroke. Women who gained more than 20 kg had a multivariate-adjusted RR of total stroke of 1.73 (95% CI, 1.34-2.22) compared with those with stable weights (P for trend<.001). After controlling for hypertension, diabetes, and elevated cholesterol, women who gained more than 20 kg from age 18 years until 1976 had an RR of 1.45 (95% CI, 0.98-2.12) for ischemic stroke. Body mass index at age 18 years was not independently associated with risk of stroke, after adjustment for adult weight change.

COMMENT

In this prospective cohort study, obesity was found to have different relationships to ischemic and hemorrhagic stroke. The most obese women (BMI≥32 kg/m^2) had a 2-fold increase in the risk of ischemic stroke compared with the leanest women. For women with a BMI of 29 kg/m^2 or more, 53% of their risk of ischemic stroke could be attributed to their excess weight. Adjustment for hypertension, diabetes, and elevated cholesterol accounted for most of the risk observed, suggesting that these factors probably mediate the adverse effects of obesity. In contrast, there was a nonsignificant inverse relation between obesity and hemorrhagic stroke with the highest risk among women in the leanest BMI category. The inverse association for hemorrhagic stroke was strongest among hypertensive women and smokers. For total stroke there was a significant relationship with higher BMI. The most obese women (BMI≥32 kg/m^2) had a 60% higher risk of total stroke than the leanest women. Fatal strokes, which were predominantly hemorrhagic, showed a weak inverse relationship with BMI, while nonfatal strokes showed a significant direct relationship.

Weight gain from age 18 years until 1976 (ages 30-55 years) also was a strong predictor of ischemic and total stroke. Women who gained more than 11 kg had significantly higher risk of ischemic stroke compared with those who maintained a stable weight. In terms of attributable risk, 60.3% of ischemic strokes among women who gained 20 kg or more from age 18 years until 1976 could be attributed to their weight gain. There was a nonsignificant inverse association for weight gain and hemorrhagic stroke. Weight gain of 11 kg or more was a significant risk factor for total stroke.

The study has several strengths. This large prospective cohort has high follow-up rates, and the type of stroke has been classified carefully through medical record review using the National Survey of Stroke criteria.[20] Although the data on weight and weight change were obtained by self-report, validation studies show a high correlation and reliability with directly measured weights.[19,23] Reliability of self-report of risk factors such as menopause,[25] smoking, alcohol use,[19] hypertension, high cholesterol,[26] and diabetes[27] has been high in this group of health professionals. Among a sample of women in this cohort, all of the self-reported hypertension, 87.5% of reports of elevated cholesterol,[26] and 98.4% of reported cases of diabetes[27] were confirmed by medical record review. Self-reported hypertension[28] and diabetes[29] were strongly associated with subsequent coronary heart disease and stroke. Because body mass index is an imperfect measure for adiposity there may be some misclassification, which may tend to underestimate the true association. Since our population is somewhat leaner than the average US population, our results may underrepresent the risk of heavier populations.

The relationship of obesity and stroke in women has remained controversial. Relatively few studies have examined the influence of obesity on the risk of stroke in women. In the Framingham Heart Study, Hubert et al[5] followed up 2818 women for 26 years and found a strong, significant association between relative weight and the risk of ischemic stroke in women. Among women with a Metropolitan Life Insurance weight

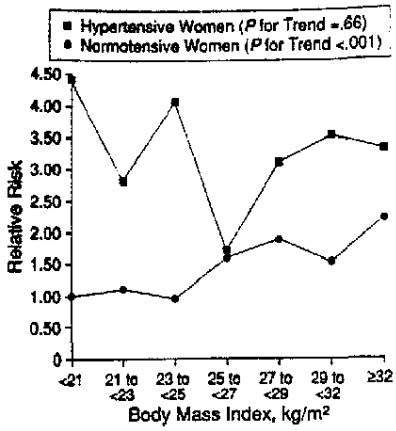

Figure 3.—Age-adjusted relative risk of ischemic stroke among hypertensive women and normotensive women by body mass index (1976-1992). Normotensive women with body mass index of less than 21 kg/m^2 are the referents. Among women who had ischemic stroke, the number of cases among hypertensive women was 203 and normotensive women, 200.

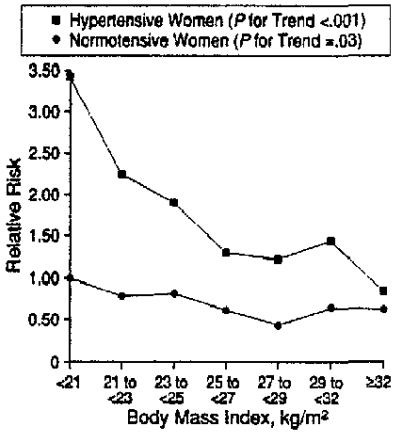

Figure 4.—Age-adjusted relative risk of hemorrhagic stroke among hypertensive women and normotensive women by body mass index (1976-1992). Normotensive women with body mass index of less than 21 kg/m^2 are the referents. Among women who had hemorrhagic stroke, the number of cases among hypertensive women was 109 and normotensive women, 182.

table relative weight greater than or equal to 130% of ideal body weight, the RR for ischemic stroke was 4.4 for those younger than 50 years and 2.7 for those aged 50 years or older compared with those whose weight was less than 110% of ideal body weight. In a cohort of 7060 women in Denmark, BMI was significantly higher among women who had strokes than women in the control group; although when examined as a continuous variable in multivariate analyses, BMI was not statistically significant.[8]

Several studies that have shown no association between obesity and stroke

Table 3.—Multivariate Relative Risks (RR) and 95% Confidence Intervals (CI) for Ischemic, Hemorrhagic,* and Total† Stroke by Category of Weight Change (From Age 18 Years to 1976) in a Cohort of US Women in the Nurses' Health Study

	Weight Change Category (kg), From Age 18 Years to 1976							
	Loss >10.9 RR (95% CI) (32 692 Person-Years)	Loss 5-10.9 RR (95% CI) (84 351 Person-Years)	Gain/Loss <5 Referent (530 824 Person-Years)	Gain 5-7.9 RR (95% CI) (220 295 Person-Years)	Gain 8-10.9 RR (95% CI) (152 609 Person-Years)	Gain 11-19.9 RR (95% CI) (246 479 Person-Years)	Gain >19.9 RR (95% CI) (116 620 Person-Years)	Trend Test‡ *P* Value
Ischemic Stroke								
No. of cases (n=346)	7	16	90	49	40	85	59	...
Age-adjusted	1.22 (0.57-2.53)	1.08 (0.64-1.84)	1.00	1.18 (0.83-1.67)	1.26 (0.86-1.84)	1.54 (1.14-2.07)	2.17 (1.56-3.02)	<.001
Model 1§	0.75 (0.33-1.71)	0.86 (0.50-1.48)	Referent	1.26 (0.88-1.78)	1.36 (0.93-1.98)	1.69 (1.26-2.29)	2.52 (1.80-3.52)	<.001
Model 2‖	0.73 (0.30-1.76)	0.83 (0.47-1.49)	...	1.13 (0.77-1.65)	1.15 (0.76-1.74)	1.60 (1.16-2.21)	2.28 (1.59-3.26)	<.001
Hemorrhagic Stroke*								
No. of cases (n=200)	2	20	73	35	22	34	14	...
Age-adjusted	0.43 (0.11-1.69)	1.58 (1.03-2.74)	1.00	1.06 (0.71-1.58)	0.88 (0.55-1.42)	0.81 (0.54-1.22)	0.67 (0.38-1.18)	.06
Model 1	0.33 (0.08-1.41)	1.44 (0.85-2.41)	Referent	1.16 (0.77-1.74)	1.00 (0.62-1.63)	0.95 (0.63-1.43)	0.86 (0.48-1.53)	.20
Model 2	0.34 (0.08-1.55)	1.38 (0.78-2.42)	...	1.00 (0.64-1.57)	1.00 (0.61-1.67)	0.77 (0.48-1.23)	0.72 (0.38-1.38)	.14
Total Stroke								
No. of cases (n=672)	16	40	206	102	70	149	89	...
Age-adjusted	1.22 (0.71-1.58)	1.19 (0.85-1.67)	1.00	1.08 (0.95-1.38)	0.98 (0.74-1.29)	1.20 (0.97-1.49)	1.47 (1.14-1.89)	.03
Model 1	0.78 (0.45-1.36)	0.98 (0.69-1.39)	Referent	1.15 (0.91-1.47)	1.06 (0.81-1.40)	1.34 (1.08-1.66)	1.73 (1.34-2.22)	<.001
Model 2	0.78 (0.43-1.42)	1.00 (0.69-1.46)	Referent	1.06 (0.81-1.38)	1.00 (0.74-1.36)	1.27 (1.00-1.60)	1.58 (1.20-2.09)	<.001

*Hemorrhagic stroke includes both subarachnoid and intraparenchymal hemorrhages.
†Total stroke includes strokes of unknown subtype, in addition to ischemic and hemorrhagic strokes.
‡Mantel-extension test for *P* value trend.
§Model 1 is adjusted for age (5-year categories), smoking (never, former, current: 1-14, 15-24, ≥25 cigarettes/d), oral contraceptive use (never, former, current), menopausal status (premenopausal, postmenopausal), hormone replacement therapy (never, former, current), and time period, with follow-up from 1976 to 1992.
‖Model 2 is adjusted for variables in model 1 and aspirin use (<1, 1-6, ≥7 tablets/wk), physical activity (<1, 1, 2, 3, ≥4 vigorous episodes/wk), antioxidant score (quintiles, diet and supplements), and alcohol use (0, <1.5, 1.5-4.9, 5.0-14.9, ≥15 g/d), with follow-up from 1980 to 1992 (n=315 ischemic, 174 hemorrhagic, and 599 total strokes).

in women have significant methodological limitations. Lapidus et al[9] found no association between BMI and stroke in a cohort of 1462 women in Göthenburg, Sweden, but this analysis was limited by only 13 cases of stroke. A study of 2773 elderly men and women in Chicago failed to find an association between adiposity and stroke.[10] This analysis controlled for hypertension and diabetes, both of which may have directly mediated the effects of obesity. In the Iowa Women's Study, women in the highest BMI tertile had an age-adjusted RR of 1.7 for self-reported stroke after 2 years of follow-up. Women in the highest tertile of both BMI and waist-to-hip ratio had a multivariate adjusted RR of 2.1, although the risk of BMI alone was not significant after adjustment for waist-to-hip ratio and other risk factors.[11] In a cohort of 30 330 women in Norway, BMI was weakly associated with stroke mortality, and there was a suggestion of increased risk in women with the lowest BMI.[12] However, no adjustment was made for smoking, and fatal strokes are more often hemorrhagic than ischemic. Many of the previous studies of obesity and stroke in women have failed to classify type of stroke or have had few stroke end points.

In men, a number of studies support an association between obesity and increased risk of stroke, especially of ischemic subtype. In the Honolulu Heart Program, nonsmoking men in the highest tertile of BMI at age 25 years had an RR of 2.1 for thromboembolic stroke in the subsequent 22 years of follow-up.[13] A direct and incremental effect of BMI on stroke mortality was observed in the Whitehall Study, with a 2- to 3-fold increased risk among men with a BMI of 24 kg/m² or more.[14] In a study of Seventh-Day Adventists, the leanest men had a 40% decrease in subsequent cerebrovascular mortality.[15] Adiposity was also a risk factor for nonfatal stroke in a long-term follow-up study of male college alumni.[17] However, other studies have failed to find an association between obesity and stroke in men.[30-34] Although weight gain has been found to be a significant risk factor for cardiovascular disease,[2,4,5] only 1 study in men has examined the effect of weight change on stroke. Obesity at age 20 years and weight gain of more than 9 kg each increased the age-adjusted risk of subsequent cerebrovascular disease in US Army veterans.[18]

Abdominal adiposity may be an additional risk factor for stroke.[11,30] However, our study could not yet examine the relationship of abdominal obesity because waist and hip measurements were only recently collected in this cohort. In comparison with coronary heart disease, the risk estimates for obesity and ischemic stroke in our study are of a smaller magnitude. In this same population the risk of coronary heart disease was increased 3-fold among women with a BMI of 29 kg/m² or more compared with those with a BMI of less than 21 kg/m². However, other risk factors, such as serum cholesterol level, have different relationships for cerebrovascular and ischemic heart disease, suggesting partially different pathways and mechanisms for the 2 diseases.

Other studies also have suggested an increased risk of hemorrhagic stroke among the leanest men and women. Tanaka et al[35] found the highest risk of hemorrhagic stroke among Japanese men and women in the lowest weight strata, although the overall trend was nonsignificant. In an analysis of 187 patients with subarachnoid hemorrhage that occurred in a community-based cohort in Finland, BMI was inversely associated with the risk of subarachnoid hemorrhage. Lean BMI greatly increased the risk of subarachnoid hemorrhage among current smokers and those with hypertension.[36] Low serum cholesterol (<4.1 mmol/L [<160 mg/dL]), which may be more prevalent among the lean, also has been associated with increased risk of hemorrhagic strokes.[37,38] Low serum cholesterol may be associated with increased blood vessel fragility or altered endothelial function.

Residual confounding or bias by preexisting conditions or smoking would be an alternative explanation for the apparent increased risk of hemorrhagic stroke among the lean women. However, excluding the first 4 years of follow-up to minimize the effects of preexisting illness did not significantly change our

results. Several studies have reported an increased risk of cardiovascular disease among lean hypertensive men or women[39,40]; however, in analyses restricted to people who were never smokers, the apparent inverse association was eliminated.[41-43] Similarly, in our study, the inverse association between BMI and hemorrhagic stroke was present only among smokers. In our analyses of hemorrhagic stroke restricted to women who were never smokers, trends became nonsignificant for both hypertensive women (P for trend=.96) and normotensive women (P for trend=.42), which suggests that residual confounding by or interaction with smoking may be a possible explanation for the findings.

Stroke remains the third leading cause of death in the United States[44] and is a major cause of disability and morbidity. Since effective therapies for stroke are few, identifying preventable stroke risk factors assumes even greater importance. Our study demonstrates that obesity increases the risk of total stroke but has different associations with ischemic and hemorrhagic stroke. Failure to analyze stroke subtypes may partially explain discrepant reports in the literature. Our study provides evidence that in women weight gain and obesity are significant risk factors for ischemic and total stroke, but *not* hemorrhagic stroke. In older populations, with a higher proportion of ischemic strokes, the effect of obesity on total stroke may be even stronger.

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